REMARKS

Applicant has considered the non-final office action mailed May 13, 2009 in connection with the Application.

Amendments to the Claims

Claims 1 – 4, 6 – 9, 15, 16, 26, 29, 48, 49, 54, 55, and 57 – 76 are pending in the Application. In the instant section, it is to be assumed that reference herein to a single portion of the specification in support of a particular amendment or new claim, is not to preclude the existence of additional support for that amendment or claim, but located elsewhere in the specification and drawings, and not specifically referenced herein.

Claim 57 is amended to include polyvinylidene fluoride (PVDF) among the list of recited substances; support for this amendment can be found at least at page 27, line 2, of the specification of the Application.

Claims 1 and 59 is amended to attend to matters of antecedent basis.

Accordingly, no new matter is introduced by way of the claim amendment herein and entry thereof is respectfully requested.

Applicant's Statement of the Substance of the Interview

Applicant's representative, the undersigned, thanks Examiner Cook for courtesies extended during a telephonic interview ("the Interview"), which took place on September 10, 2009. Also attending the Interview by telephone were inventor, Professor Paul Denny, and Fish & Richardson P.C. Technology Specialist, Song Ren, Ph.D.

During the Interview, Applicant's representative addressed the outstanding rejections in the May 13, 2009 office action, and advanced an analysis of the Seeman reference in which the reference's failure to teach or disclose a predictive method was emphasized.

The examiner acknowledged having understood Applicant's reasoning but stated that she expected to have to carry out a new search on the basis of a renewed interpretation of Seeman.

Applicant's representative also asked Examiner Cook to reconsider Applicant's arguments (already of record) as to the relevance of the Akintoye reference. The Examiner asked for those arguments to be resubmitted when responding to the May 13, 2009 office action.

REJECTIONS OF THE CLAIMS

Rejections under 35 U.S.C. § 103

The Examiner has rejected the claims as allegedly obvious over two or more references in combination.

Applicable legal standard

For conciseness, Applicant prefaces the following remarks with a statement of the prevailing legal standard, applicable to all rejections.

The framework under which obviousness of a patent claim is judged was set forth by the U.S. Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), and is as follows. Under § 103:

- the scope and content of the prior art are to be determined;
- differences between the prior art and the claims at issue are to be ascertained; and
- the level of ordinary skill in the pertinent art resolved.

Based upon the answers to these factual enquiries, the obviousness or nonobviousness of the claimed subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might also be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Accordingly, and at a minimum, in order to establish obviousness of a claim, the prior art reference, or references when combined, must teach or suggest each and every limitation of the claimed invention. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Furthermore, and in instances where each and every limitation of the claimed invention can be found in a combination of references, an analysis of an apparent reason to combine the known elements in the fashion claimed should be made explicit. *KSR Int'l. Co. v. Teleflex Inc.*, (550 U.S. 398, 127 S. Ct. 1727 (2007)).

Additionally, dependent claims are nonobvious under 35 U.S.C. § 103 "if the independent claims from which they depend are nonobvious." *In re Fine* 837 F.2d 1071; 5 USPQ.2d 1596; MPEP 2143.03.

Applicant's claims

The pending claims are based on the measurements of affinities of two or more lectins for various lectin-binding components of saliva from a subject, and correlating the binding affinities with the risk of dental caries in the subject.

Examiner's rejection of claims 1 – 4, 9, 16, and 29, and cited references

The Examiner has rejected claims 1 – 4, 9, 16, and 29, under 35 U.S.C. § 103(a) as allegedly being obvious over Seemann *et al.*, *Caries Research*, 2001, Vol. 35, pages 156 – 161 ("Seemann"), in view of Akintoye *et al.*, *Archives of Oral Biology*, Vol. 47, 2002, pages 337 – 345 ("Akintoye") and further in view of Hartles, *The American Journal of Clinical Nutrition*, Vol. 20, No. 2, February 1967, pages 152 – 156 ("Hartles").

The Examiner states that Seemann discloses a method of evaluating high and low caries susceptibility in children and that, although Seemann differs from the instant claims at least because it does not specifically teach evaluations based on the measurement of two or more lectins, the Examiner points out that Akintoye discloses methods to characterize salivary APP (adhesion promoting protein) in caries-prone and caries-free individuals utilizing "various lectins". Specifically, Akintoye utilized several lectins to determine the partial glycosylation patterns of carbohydrates on salivary proteins. Since Akintoye is supposedly silent with respect to a link between "carbohydrates and dental caries risk", the Examiner offers Hartles for disclosing that "carbohydrate consumption is involved in the production of caries."

As further discussed hereinbelow, the remaining claims are also rejected over Seemann, Akintoye and Hartles, in combination with one or more other references. Accordingly, Applicant begins with remarks that address the combination of Seemann, Akintoye and Hartles alone in order to emphasize core aspects of the arguments that are also applicable to all of the rejections.

Applicant's Response to Examiner's rejection

First, as noted in the Interview, claim 1 in the instant application recites a method of *predicting* the risk of dental caries in a subject, whereas Seemann investigates whether, over a period of time, there is a reliable differentiation in the binding inhibition of PNA between

subjects previously designated as Caries Resistant (CR) and those designated as Caries Susceptible (CS), the designation having been based on other means (than current measurements of dental decay or of lectin binding). Therefore, Applicant's claimed method is a *prospective* evaluation, whereas Seeman engages in a *retrospective* analysis. As such, Seemann does not describe a predictive test of caries risk. The following aspects of the Seeman disclosure (as elaborated upon during the Interview) make this distinction apparent to a skilled artisan.

The title of Seemann ("Differences in the Salivary Glycan Pattern between Children with High and Low Caries Susceptibility") accurately sums up the scientific results purported to be shown in Seemann: that there may be differences in salivary glycan patterns between children shown (by other indicia) to have either high or low caries susceptibility. In other words, Seemann attempts the reverse of the method claimed in the instant application: Seemann attempts to show that, given an objective classification of children as either CS or CR (such as by counting decayed or filled teeth) at a particular timepoint, is there a salivary glycan that is more prevalent in one set than in the other, and, if so, does it remain prevalent over a sustained period of time (such as 2 years)? The Examiner recognizes this and cites to Table 1 of Seemann:

> The patient samples were measured … against control saliva samples of a known concentration (see baseline, 2 year caries, and salivary flow in Table 1 on page 159). The saliva of caries free subjects (CR) showed a higher binding inhibition against the PNA lectin [than] the saliva of children with DMFT greater than 4 (CS). See page 158 2nd column and Table 1.

May 13, 2009 Office Action, at page 3.

It is instructive to examine Table 1 of Seemann in detail. Seemann suggests that, of those tested, PNA may be a probe for a particular salivary glycan, but does not show that, given a measurement of a lectin binding event against a subject's saliva, that the subject's likelihood of developing caries can be predicted. In particular, Seemann does not maintain a constant classification of members of the two populations so that one could deduce whether the measurement of PNA binding correlates with a *change* over time. The section of Seemann entitled "Data Analysis" (on p.158, first column) describes how subjects whose classification changes with time (based on various dental indices) are removed from their respective patient pools. This aspect of the study alone undermines its scientific credibility as a method of

prediction, since it is impossible to say, based on the reported data, which members of the combined patient pool who were CR at Step 1 could be classified as members of the patient pool who were CS in Step 2 (a classification that would be critical to a predictive method). A method of prediction should be able to say, given a patient's level of bound lectin(s) at the beginning of the study, what is likely to be their level of caries incidence at the next time point.

A further problem with the data in Table 1 of Seemann is that it does not actually support the reference's own conclusion that there is a meaningful correlation between PNA binding and CR/CS classification. The fact that the error bars on Resting PNA binding inhibition cause both subject sets to overlap with one another makes it impossible to conclude with reasonable certainty that PNA binding inhibition *per se* is correlated at all with dental caries progression or onset in the manner the reference purports. Consider, for example, a subject whose measured Resting PNA binding inhibition (% of standard) is 20%. Such a patient's measurement falls well within the ranges reported in Table 1 of Seemann for both the CR and CS sets at both Step 1 (28 ± 14; 20 ± 8 respectively) and Step 2 (28 ± 11; 19 ± 7 respectively). Such a patient can hardly be assessed with any reliability as being either a patient with high susceptibility to caries, or one with low susceptibility. Therefore, based on the only reported data in Seemann, an artisan of ordinary skill would not be able to conclude that measurements of PNA inhibition alone would provide the basis for a test of caries susceptibility or risk.

Furthermore, the binding assay that underpins the reported data in Seemann is distinctly different from the binding protocol recited in the instant application. As discussed hereinabove, Seemann describes a competitive inhibition assay in which a glycoconjugate is immobilized on a surface. The immobilized glycoconjugate is contacted with a solution containing saliva and a purified lectin. Carbohydrate portions of glycoproteins in saliva compete with the immobilized glycoconjugate for binding the purified lectin and mean that less lectin becomes bound to the surface, a diminution that itself can be quantified. In contrast, in the claimed method, the direct binding of lectins to components of saliva is quantified. There would be no expectation on the part of an artisan of ordinary skill to substitute such a direct binding method for the competitive binding assay described by Seeman, and to be able to achieve a method according to Applicant's claims.

Finally, regarding the secondary references cited to by the Examiner, Applicant respectfully points out that neither Akintoye nor Hartles discloses a method for predicting the risk of dental caries based on lectin binding in salivary sample. Applicant further incorporates by reference herein the remarks of record in Applicant's Reply of February 9, 2009 in the Application, as directed to the combination of Seemann and Akintoye. In particular, and as referenced in the Interview described herein, Applicant respectfully reiterates that Akintoye does not teach or disclose the use of multiple lectins in distinguishing between "caries-active" or "caries-resistant" individuals.

Notwithstanding the statement in the Abstract of Akintoye ("Antibodies to APP demonstrated no difference in the immunoreactive pattern of APP from saliva of caries-active or caries-resistant individuals"), Akintoye is of limited relevance to the claims of the Application because it describes characterization of a protein (accomplished only in part by lectin blotting against the pendant carbohydrate groups on the protein's surface) and fails to make any connection between the lectin-binding components of an individual's saliva and caries risk. Applicant asks the Examiner to note, from the cited portion on p.338 of Akintoye, that Akintoye's "purpose … was to purify and further characterize a human submandibular salivary APP and identify its immunological pattern in caries-prone and caries-free individuals." This was done against the backdrop that APP was thought to be "important *in vivo* in the initial colonization of the enamel surfaces [of teeth]" because it was known that the bacterium *S. mutans* ("a primary agent in the aetilogy of dental caries") itself has a "highly specific" binding interaction with APP. Thus Akintoye describes aspects of a mechanism of bacterial attachment to tooth surfaces in relation to caries, and not any possible connection between the other lectin-binding constituents of an individual's saliva and caries.

Thus, for at least the foregoing reasons, claim 1 is not obvious over the three cited references. Since claims 2 – 4, 9, 16, 26, and 29 depend on claim 1, they are also not obvious over these references. Applicant respectfully requests that the rejection be removed.

The rejection over Seemann, Akintoye, Hartles, and Foster

The Examiner has rejected claims 49, 54 and 55, reciting kits, under 35 U.S.C. § 103(a) as allegedly being obvious over Seemann in view of Akintoye and Hartles, and further in view of

Foster *et al.*, U.S. Patent No. 4,444,879 ("Foster"), for reasons stated hereinabove, and because Foster discloses assay reagents in a kit form.

As addressed hereinabove, Seemann, Akintoye and Hartles do not disclose a method for predicting the risk of dental caries based on lectin binding in salivary sample, and (as the Examiner notes) also do not describe a kit for carrying out such a method. Foster does not disclose the teachings that are missing from Seemann, Akintoye and Hartles; instead, Foster only discloses kits generally for assay reagents.

Thus, Claims 49, 54 and 55 are not obvious over the four cited references in combination, and Applicant respectfully requests that the rejection be withdrawn.

The rejection over Seemann, Akintoye, Hartles, and Shibuya

The Examiner has rejected claim 15 (depending from claim 1), reciting a method, and claims 57 – 60, and 69, reciting an assay device, under 35 U.S.C. § 103(a) as allegedly being obvious over Seemann in view of Akintoye and Hartles, and further in view of Shibuya *et al.*, U.S. Patent No. 4,582,795 ("Shibuya"), for reasons stated hereinabove, and because Shibuya discloses the measurement of a drop of saliva in a matrix material (device).

As addressed hereinabove, Seemann, Akintoye and Hartles do not disclose a method for predicting the risk of dental caries based on lectin binding in salivary sample, and further do not disclose an assay device for carrying out the same. Shibuya does not disclose the teachings that are missing from Seemann, Akintoye and Hartles; instead, Shibuya only discloses a method and device for rapid *diagnosis* of dental caries utilizing a very small amount of saliva (drop).

Thus, claims 15, 57 – 60 and 69 are not obvious over the four cited references in combination, and Applicant respectfully requests that the rejection be withdrawn.

The rejection over Seemann, Akintoye, Hartles, and Sharon

The Examiner has rejected claims 6 – 8, 48, 75, and 76, reciting methods, under 35 U.S.C. § 103(a) as allegedly being obvious over Seemann in view of Akintoye and Hartles, and further in view of Sharon, *Adv. Exp. Med. Biol.*, Vol. 408, pages 1 – 8, 1996 ("Sharon"), for reasons stated hereinabove, and because Sharon discloses that the carbohydrate lectin binding interaction is known and supposedly linked to various diseases.

As addressed hereinabove, Seemann, Akintoye and Hartles do not disclose a method for predicting the risk of dental caries based on lectin binding in salivary sample. Sharon does not disclose the teachings that are missing from Seemann, Akintoye and Hartles; instead, Sharon only discloses carbohydrate-lectin interactions in infectious diseases (and does not identify caries specifically).

Thus, claims 6 – 8, 48, 75, and 76 are not obvious over the four cited references in combination, and Applicant respectfully requests that the rejection be withdrawn.

The rejection over Seemann, Akintoye, Hartles, and Hume

The Examiner has rejected claims 61 – 68, reciting methods, under 35 U.S.C. § 103(a) as allegedly being obvious over Seemann in view of Akintoye and Hartles, and further in view of Hume, *Journal of Dental Education*, Vol. 57, No. 6, 6/1993, pages 439-443 ("Hume"), for reasons stated hereinabove, and because Hume discloses disease risk levels and severity.

As addressed hereinabove, Seemann, Akintoye and Hartles do not disclose a method for predicting the risk of dental caries based on lectin binding in salivary sample. Hume does not disclose the teachings that are missing from Seemann, Akintoye and Hartles; instead, Hume only discloses that caries can be evaluated with multiple factors to determine whether the disease process begins, progresses, stops or reverses.

Thus, claims 61 – 68 are not obvious over the four cited references in combination, and Applicant respectfully requests that the rejection be withdrawn.

The rejection over Seemann, Akintoye, Hartles, Shibuya, and Lindmo

The Examiner has rejected claims 70 – 74, reciting methods (depending directly or indirectly from claim 1), under 35 U.S.C. § 103(a) as allegedly being obvious over Seemann in view of Akintoye and Hartles, further in view of Shibuya, and further in view of Lindmo, U.S. Patent No. 5,585,241 ("Lindmo"), for reasons stated above, and because Lindmo discloses a flow cytometry method of detecting analytes via microbeads (particles) carrying a specific binding partner.

As addressed hereinabove, Seemann, Akintoye and Hartles do not disclose a method for predicting the risk of dental caries based on lectin binding in salivary sample. Neither Shibuya

nor Lindmo discloses such a method. Instead, as discussed hereinabove, Shibuya only discloses a method and device for rapid diagnosis of dental caries utilizing a very small amount of saliva (drop). Lindmo only discloses a flow cytometry assay that could use lectin and carbohydrate as analyte and binding partner pair, but does not disclose the method for predicting the risk of dental caries.

Thus, claims 70 – 74 are not obvious over the five cited references in combination, and Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

In view of the above remarks, Applicant respectfully submits that the subject application is in good and proper order for allowance. Withdrawal of the Examiner's rejections and early notification to this effect are earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 839-5070.

No fee is believed owed in connection with filing of this amendment and reply. However, should the Commissioner determine otherwise, the Commissioner is authorized to charge any underpayment or credit any overpayment to Fish & Richardson P.C. Deposit Account No. 06-1050 (Ref. No. 19644-0005US1) for the appropriate amount.

Respectfully submitted,

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